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CANMAT 2023 UPDATE:
CLINICAL GUIDELINES FOR THE MANAGEMENT OF MDD IN ADULTS

QUESTION 7:

What Should Be Done When a Patient is Not Better?

Inadequate response is a common clinical challenge

After 8 weeks of antidepressant monotherapy:

~half of patients with MDD achieve a response*

~one-third attain full symptom remission

Only one-quarter of nonremitters who receive a 2nd pharmacological treatment achieve remission

Remission rates are higher in first-treatment patients, but almost half will not achieve remission with ADTs after 6 months

*Defined as >50% reduction in symptom severity.
ADT, antidepressant; MDD, major depressive disorder.
Lam RW, Kennedy SH, Adams C, et al. Can J Psychiatry. 2024 Sep;69(9):641-87.

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Factors contributing to poor response to initial treatment

Several clinical, comorbidity and medication factors contribute to insufficient treatment response

Clinical factors

- Incorrect diagnosis
  (e.g., bipolar disorder)
- Demographics
  (e.g., older age, female sex)
- Illness characteristics
  (e.g., younger age of onset, higher severity, increased number/ duration of MDEs, trauma history)
- Acute or chronic stressors

Comorbidities

- Psychiatric
  (e.g., ADHD, anxiety, personality or substance use disorders)
- Nonpsychiatric
  (e.g., anemia, obesity, sleep apnea, thyroid disease, etc.)

Medication factors

- Inadequate dose
- Inadequate duration
- Side effects
- Poor adherence
- Pharmacogenetic variability
  (e.g., rapid or slow drug metabolism)

ADHD, attention deficit/hyperactivity disorder; MDE, major depressive episode.

Lam RW, Kennedy SH, Adams C, et al. Can J Psychiatry. 2024 Sep;69(9):641-87.

What is ‘treatment-resistant depression’ (TRD)?

Most commonly refers to **failure to respond to ≥2 ADT trials** at therapeutic dose and adequate duration

Limitations

“Failure” is **inconsistently defined** and **does not account for partial response** or residual symptoms

“Resistance” **suggests futility** and may **discourage further interventions**

Neglects **psychological and neurostimulation** treatments

Assumes switching is preferred over add-on strategies as an initial strategy

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ADT, antidepressant; TRD, treatment-resistant depression.
Lam RW, Kennedy SH, Adams C, et al. Can J Psychiatry. 2024 Sep;69(9):641-87.

What is ‘difficult-to-treat depression’ (DTD)?

- Term proposed to better characterize the **collaborative journey** when standard treatments have not been effective
- Defined as **persistent depression** that has **failed numerous standard treatments**
- More **supportive, hopeful and holistic** term than TRD

DTD, difficult-to-treat depression; QoL, quality of life; TRD, treatment-resistant depression.

Lam RW, Kennedy SH, Adams C, et al. Can J Psychiatry. 2024 Sep;69(9):641-87.

Clinical reassessment is a key first step for poor response

- Re-evaluate the diagnosis (e.g., missed diagnosis of bipolar disorder)
- Assess for psychiatric comorbidities (e.g., ADHD, anxiety, substance use disorders, personality disorders)
- Evaluate adherence to treatment
- Consider other biological and psychosocial factors that may interfere with treatment response

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ADHD, attention deficit/hyperactivity disorder.

Lam RW, Kennedy SH, Adams C, et al. Can J Psychiatry. 2024 Sep;69(9):641-87.

Clinical strategies for poor response to initial ADT treatment

Laboratory investigations: to rule out medical factors potentially contributing to persistent symptoms

Pharmacogenetic testing: to identify pharmacokinetic reasons for poor response or adverse effects

Systematic, sequential and MBC may enhance outcomes

LoE, Level of Evidence Level 1 Level 2 Level 3 Level 4

ADT, antidepressant; MBC, measurement-based care.

Lam RW, Kennedy SH, Adams C, et al. Can J Psychiatry. 2024 Sep;69(9):641-87.

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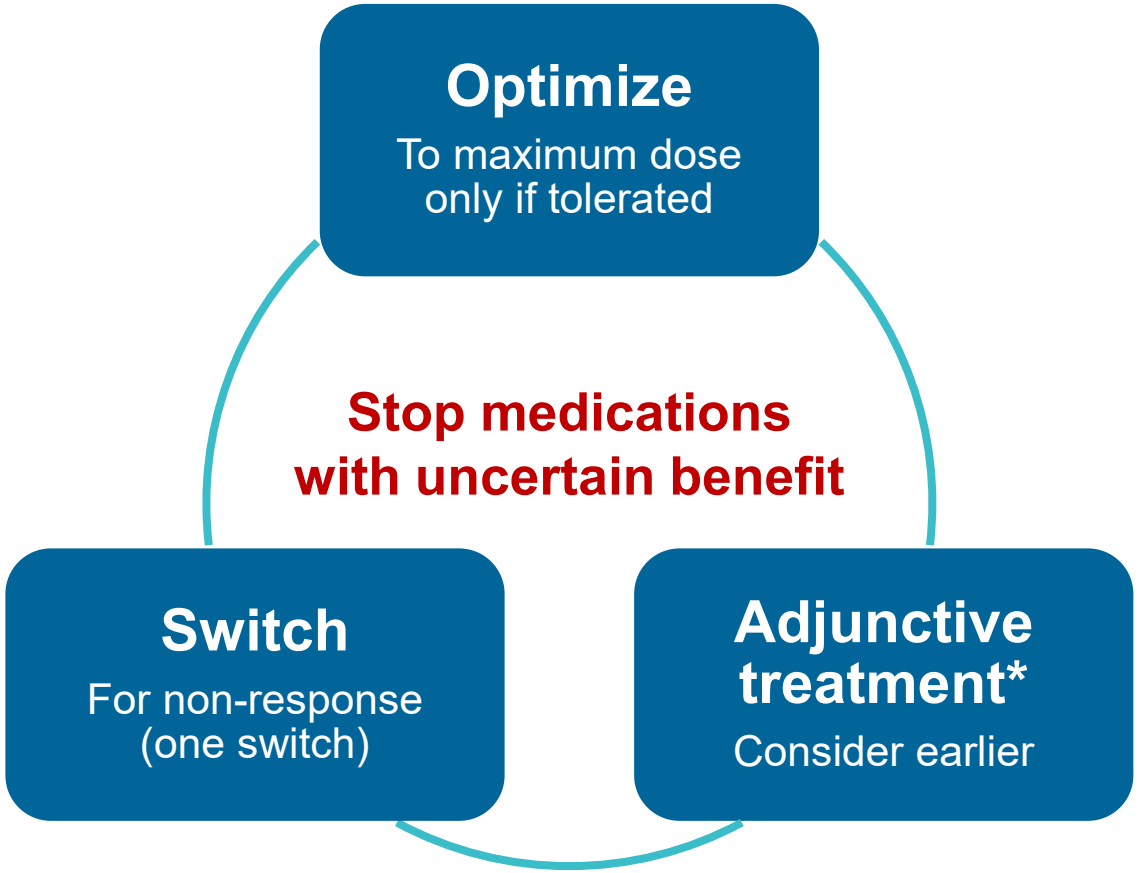
Medication strategies for poor response to initial ADT treatment



- Given the **limited evidence**, sequencing of treatments should be based on a **collaborative approach** that integrates:
  - ✓ Prior treatment history
  - ✓ Strength of evidence for efficacy
  - ✓ Potential for adverse events
  - ✓ Patient preference

LoE, Level of Evidence — Level 1 — Level 2 — Level 3 — Level 4

*Addition of psychological treatments, adjunctive medication, or neuromodulation (for treatment-resistant depression).
ADT, antidepressant.

Lam RW, Kennedy SH, Adams C, et al. Can J Psychiatry. 2024 Sep;69(9):641-87.

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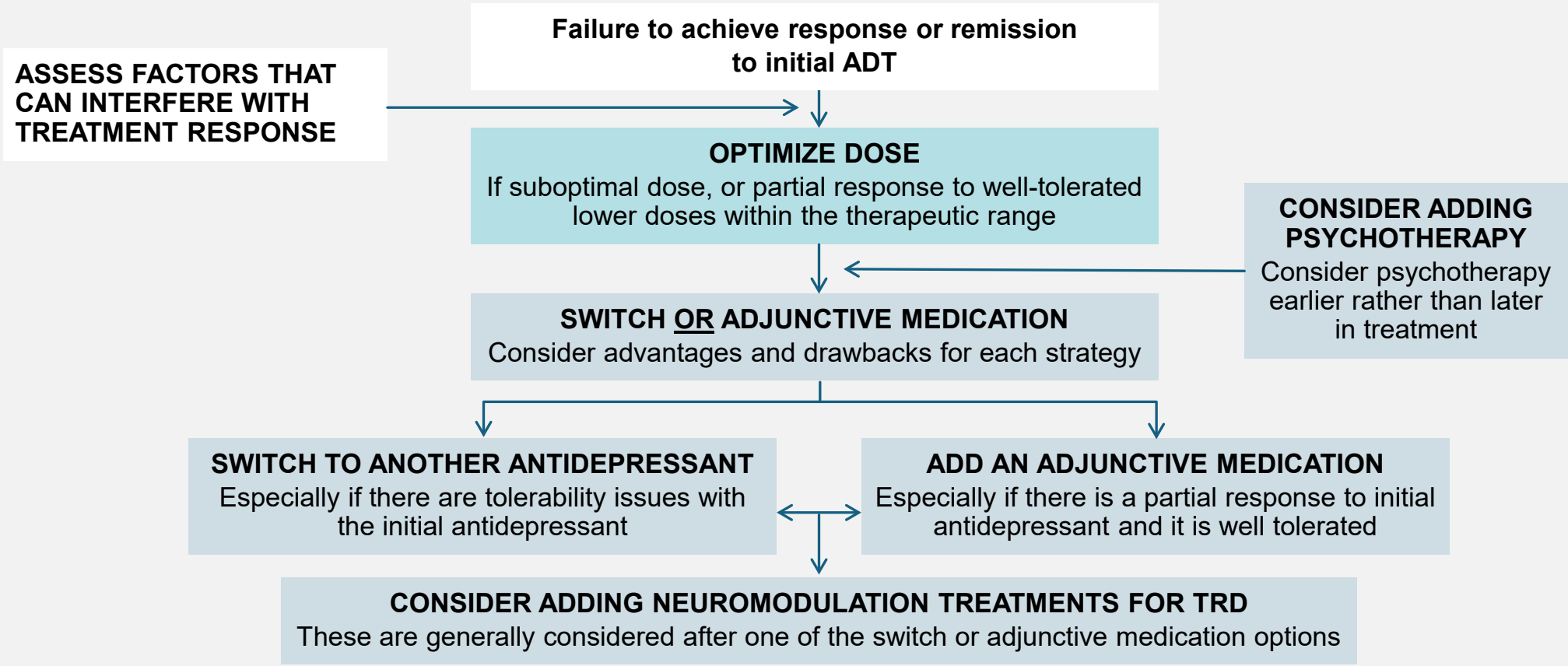
Algorithm for sequential treatment after suboptimal response



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ADT, antidepressant; TRD, treatment-resistant depression.

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Dose optimization is an important first step

Consider optimizing if **subtherapeutic dose or partial response** to well-tolerated lower doses within the therapeutic range

Higher than minimal therapeutic doses are **more effective** but **less well tolerated**

Increasing the dose for nonresponse must be balanced against **increasing side effect burden** and **poorer adherence**

LoE, Level of Evidence Level 1 Level 2 Level 3 Level 4

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Lam RW, Kennedy SH, Adams C, et al. Can J Psychiatry. 2024 Sep;69(9):641-87.

Considerations for switching vs adjunctive strategies

Switching

When there is <u>no response</u> to initial ADT or <u>tolerability issues</u>

- Diminishing response rates beyond the 1st switch

Adjunctive

Consider <u>earlier</u> if there is a <u>partial response</u> to initial ADT and it is <u>well tolerated</u>

- Greater evidence for efficacy and shorter time to response or remission, but higher side effect burden than ADT monotherapy

Decision informed by comprehensive review of **previous medication trials**, **major side effects** experienced, and whether there is **partial response**

LoE, Level of Evidence  Level 1  Level 2  Level 3  Level 4

ADT, antidepressant.

Lam RW, Kennedy SH, Adams C, et al. Can J Psychiatry. 2024 Sep;69(9):641-87.

When and how should ADTs be switched?

Early improvement* within the first 4 weeks predicts a later response

Lack of early improvement* by 4 weeks predicts low likelihood of response or remission at 8 to 12 weeks

Summary Recommendations for Switching	LoE
• Select a 1st-line ADT with **evidence for superior efficacy** and **favourable tolerability**	
• **Crossover "X" switch** (i.e., slowly taper 1st ADT while slowly titrating up 2nd ADT)	
• **Washout "V" switch** if less urgency or history of discontinuation symptoms (i.e., taper and discontinue 1st ADT before starting 2nd ADT)	

Consult **online switching tools** (e.g., SwitchRx.com) for advice on titration and switching

LoE, Level of Evidence — Level 1 — Level 2 — Level 3 — Level 4

*Defined as ≥20% reduction in scores on a symptom rating scale.
ADT, antidepressant.

Lam RW, Kennedy SH, Adams C, et al. Can J Psychiatry. 2024 Sep;69(9):641-87.

Benefits and drawbacks of adjunctive medication

Benefits

- Retains partial gains from the initial ADT
- Avoids discontinuation symptoms
- Adds complementary mechanism of action
- Faster onset of response
- Target specific residual symptoms or side effects

Limitations

- Possible additive side effects
- Increased cost of treatment
- Potential drug-drug interactions
- May decrease adherence
- Little evidence for maintenance treatment

Adding a low-dose adjunctive agent may accrue fewer side effects than increasing a single ADT to higher doses

LoE, Level of Evidence — Level 1 — Level 2 — Level 3 — Level 4

ADT, antidepressant.

Lam RW, Kennedy SH, Adams C, et al. Can J Psychiatry. 2024 Sep;69(9):641-87.

How is an adjunctive medication selected?

Adjunctive strategies should be considered earlier in the treatment algorithm, after limited response to the 1st or 2nd ADT trial

Considerations for selection of adjunctive agent

Evidence for efficacy

Tolerability (of the adjunctive agent and continued ADT)

Potential drug-drug interactions

Pharmacogenetic tests (if available)

Target specific residual symptoms and/or side effects

Tip: Discontinue medications with unclear benefits to minimize polypharmacy

LoE, Level of Evidence  Level 1  Level 2  Level 3  Level 4

MDD, major depressive disorder; MDE, major depressive episode.

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Recommendations for adjunctive treatments (part 1)

Line of Treatment	Adjunctive Agent	Target Dose[1]	Level of Evidence
1st Line	Aripiprazole	2-10 mg	
	Brexpiprazole*	0.5-2 mg	
2nd Line	Bupropion	150-450 mg	
	Intranasal esketamine*	56-84 mg IN	
	IV racemic ketamine*	0.5-1.0 mg/kg IV	
	Olanzapine	2.5-10 mg	
	Quetiapine XR*	150-300 mg	
	Risperidone*	1-3 mg	
	Lithium	600-1200 mg (0.5-0.8 mmol/L)	
	Cariprazine*	1.5-3 mg	
	Mirtazapine/mianserin	30-60 mg / 30-90 mg	
	Modafinil	100-400 mg	
	Triiodothyronine	25-50 mcg	

LoE, Level of Evidence  Level 1  Level 2  Level 3  Level 4

*Change since CANMAT 2016 guidelines, based on updated evidence. See speaker notes for additional footnotes.
IN, intranasal; IV, intravenous; XR, extended release.
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Recommendations for adjunctive treatments (part 2)

Line of Treatment	Adjunctive Agent	Target Dose[1]	Level of Evidence
3rd Line	Other ADTs including TCAs	Varies	
	Stimulants	Varies	
	Lamotrigine*	100-300 mg	
	Non-IV racemic ketamine*	Varies	
	Pramipexole*	1-2 mg b.i.d.	
	Ziprasidone	20-80 mg b.i.d.	
Investigational	Psychedelic-assisted psychotherapy*	Moderate to high doses with psychotherapy	
Not recommended	Cannabis* (insufficient evidence for efficacy; risk of harms)	n/a	n/a

LoE, Level of Evidence — Level 1 — Level 2 — Level 3 — Level 4

*Change since CANMAT 2016 guidelines, based on updated evidence. See speaker notes for additional footnotes.
ADT, antidepressant; b.i.d., twice daily; IV, intravenous; TCA, tricyclic antidepressant.
Lam RW, Kennedy SH, Adams C, et al. Can J Psychiatry. 2024 Sep;69(9):641-87.

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Adjunctive psychological treatments

- 1st-line psychological agents should be considered **early in the treatment course** based on efficacy and low potential for side effects 
- **Few studies** of psychotherapy after poor response to ADTs
- **CBT** is recommended as a **2nd-line adjunctive** to medications for DTD to reduce symptoms and increase response and remission 
- **Psychedelic-assisted** psychotherapy is an **investigational** treatment*

LoE, Level of Evidence  Level 1  Level 2  Level 3  Level 4

*See CANMAT Task Force Report on serotonergic psychedelic treatments for MDD.

ADT, antidepressant; CBT, cognitive behavioural therapy; DTD, difficult-to-treat depression; MDD, major depressive disorder.

Lam RW, Kennedy SH, Adams C, et al. Can J Psychiatry. 2024 Sep;69(9):641-87.

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Adjunctive neurostimulation treatments

Good evidence for efficacy in TRD and DTD

Limited accessibility and patient burden

Generally considered after one of the switch or adjunctive medication options

DTD, difficult-to-treat depression; TRD, treatment-resistant depression.

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Back Up Slides

Risks and benefits of specific adjunctive medications (part 1)

Adjunctive Medication	LoE
Serotonin-dopamine activity modulators (low-dose AAPs) • Most consistent evidence for efficacy in DTD • More efficacious than placebo in network meta-analyses • Lower doses are used in MDD than in bipolar disorder or schizophrenia • Variable receptor and side effect profiles (acute and long-term) including weight gain	
Addition of a 2nd ADT • More favourable side effect profile but less robust efficacy vs adjunctive AAPs • More efficacious than switching in meta-analyses • Adding mirtazapine/mianserin is superior to other combinations • Evidence for bupropion from large RCTs but meta-analyses are inconclusive • Older ADTs (e.g., TCAs) have limited evidence and safety/tolerability issues	

LoE, Level of Evidence  Level 1  Level 2  Level 3  Level 4

AAP, atypical antipsychotic; ADT, antidepressant; DTD, difficult-to-treat depression; MDD, major depressive disorder; TCA, tricyclic antidepressant.

Lam RW, Kennedy SH, Adams C, et al. Can J Psychiatry. 2024 Sep;69(9):641-87.

Risks and benefits of specific adjunctive medications (part 2)

Adjunctive Medication	LoE
Newer glutamate modulators*	
• Potential for rapid onset of effects • Extensive evidence for IV racemic ketamine (single dose) • Demonstrated effectiveness of repeated infusions of IV racemic ketamine • Meta-analyses support efficacy of IN esketamine • Evidence for relapse prevention efficacy of IV racemic ketamine and IN esketamine • Rapid reduction in suicidal ideation with IV racemic ketamine and IN esketamine • Other routes of administration of racemic ketamine have mixed evidence of efficacy • Ketamine and esketamine are weight neutral	
Older glutamate modulators	
• Lamotrigine has shown higher response rates vs ADT monotherapy (meta-analysis) • Well tolerated including weight neutral, but risk of Stevens-Johnson rash	

LoE, Level of Evidence  Level 1  Level 2  Level 3  Level 4

*See CANMAT Task Force Report on use of racemic ketamine in adults with MDD.
ADT, antidepressant; IN, intranasal; IV, intravenous; MDD, major depressive disorder.
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Risks and benefits of specific adjunctive medications (part 3)

Adjunctive Medication	LoE
Stimulants	

• Mixed evidence for efficacy of amphetamines in MDD (network meta-analysis)
  • Side effects (e.g., anxiety, irritability, tremors, headaches, insomnia, weight neutral or weight loss)
  • Tolerance may develop
	

• Modafinil has consistent evidence for efficacy but small effect size • Potential pro-cognitive effects (i.e., executive functioning)	 
Other medications	
• Lithium and triiodothyronine have evidence for efficacy as adjuncts to TCAs	
• Pramipexole superior to placebo and similar to SSRIs in small RCTs	
• No RCTs for cannabis but there is evidence of worse depression outcomes	

LoE, Level of Evidence  Level 1  Level 2  Level 3  Level 4

MDD, major depressive disorder; RCT, randomized controlled trial; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Lam RW, Kennedy SH, Adams C, et al. Can J Psychiatry. 2024 Sep;69(9):641-87.